


TB/HIV: Managing the Co-Infected Patient

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Overview

- Epidemiology of TB/HIV
 - Global and U.S.
 - TB risk: effect of HIV and antiretroviral therapy
 - Drug-resistant TB and HIV: MDR-TB, XDR-TB
- Diagnosis of TB in HIV+ persons
- Treatment of TB/HIV
 - Optimal duration of therapy; relapse risk
 - Acquired rifamycin resistance
 - Drug-drug interactions
 - Immune reconstitution inflammatory syndrome (IRIS)
 - When to start HAART in TB/HIV patients
- Prevention of TB in HIV+ persons




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Global TB/HIV Epidemiology 2005

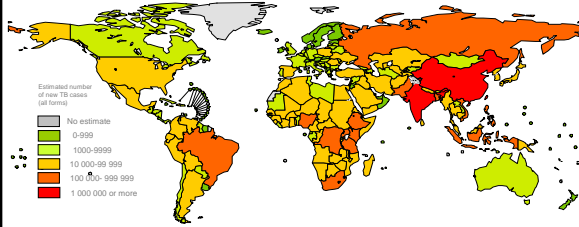
- **Estimated # new TB cases:** 8.8 million
- **Estimated # prevalent cases:** 14.1 million
- **Estimated # deaths:** 1.6 million
 - HIV-infected TB deaths: 195,000
- **Estimated # infections:** 2 billion
 - 33% of population



WHO Global TB Report 2007. WHO/HTM/TB/2007.376

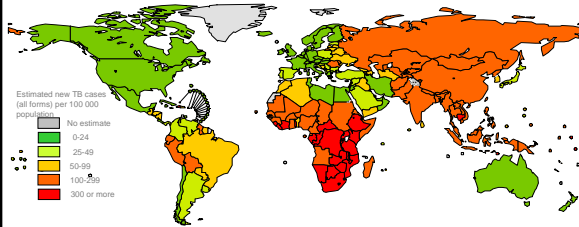
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Estimated numbers of new cases, 2005



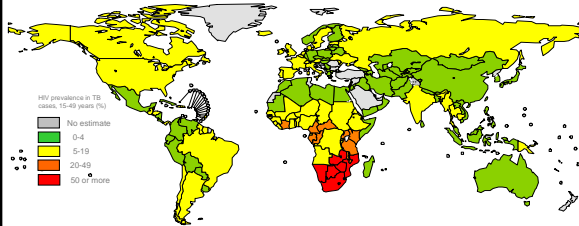
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Estimated TB incidence rate, 2005



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Estimated HIV prevalence in new TB cases, 2005



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HIV Surveillance in TB Patients Botswana, 2002

- National TB rate: 623 cases per 100,000 population
- Rapid HIV diagnostic test (Oraquick) on sputum
- March-November 2002
- 24 govt. laboratories → National TB Reference Lab
 - 2,200 sputum smear + patients
 - 219 previously treated—suspected recurrent TB
- Of the 2,419: 1,457 (60%) HIV +

HIV Infection in TB Patients United States, 1993-2005

- Proportion of TB patients with known HIV status:
 - 1993: 35%
 - 2005: 68%
- TB cases in 2005:
 - 9% HIV +
- TB patient groups at ↑ risk for HIV:
 - Injection drug users
 - Noninjection drug users
 - Homeless persons
 - Non-Hispanic blacks
 - Correctional facility inmates
 - Alcohol abusers

CD4 and TB Risk

- 1130 HIV+ without AIDS followed median of 53 months (U.S.: Pulmonary Complications of HIV Study Group). No ART
- TB risk greater with lower CD4 count
 - CD4 < 200: 1.2 TB cases per 100 p-y
 - CD4 > 200: 0.5 TB cases per 100 p-y
 - RR: 2.4 (95% CI: 1.1, 5.2)
 - Markowitz N. Ann Intern Med 1997;126:123-32
- 944 HIV+ persons receiving ART (South Africa)
 - TB risk associated only with current CD4 count (within 4 months)
 - Not age, sex, prior TB, WHO disease stage, HIV-1 RNA
 - 25% decrease in TB risk per 100 cell ↑ in CD4 count
 - Lawn SD. AIDS 2006;20:1605-12.

Viral Load and TB Risk

- 1480 HIV+ mineworkers in South Africa
- TB cases: viral load > 3 months prior to TB, and > 5 months after TB
- Controls (no TB): matched on baseline CD4 and duration of follow-up
- 30 TB cases and 56 controls
- No antiretroviral therapy; all TB cases treated

Viral Load and TB Risk

	<u>TB cases</u>	<u>Controls</u>	<u>P-value</u>
CD4 baseline	295	297	
VL baseline(log)	4.73	4.24	0.003
VL final (log)	5.02	4.34	<0.001

- Higher baseline VL in TB cases suggests that VL is a risk factor for TB, independent of CD4
- After adjusting for baseline VL + disease stage: VL ↑ 0.24 log in TB cases: could ↑ HIV disease progression, transmission
- Importance of VL suppression to ↓ TB risk, HIV progression

TB Risk in HIV-Infected Persons Without antiretroviral therapy

- Approaches 40% after recent exposure to *M. tuberculosis*
 - Daley CL NEJM 1992;326:231-5
- Approx. 10% annual risk if latently infected
 - Selwyn PA NEJM 1989;320:545-50

TB Risk in HIV-Infected Persons HAART Era

TB rate per 100,000 person-years:

	No ART	ART	HAART
U.S.	720	470(40%↓)	190 (80%↓)
S. Africa	9700		2400 (81%↓)

Jones JL. Int J Tuberc Lung Dis 2000;4:1026—AASD
Badri M. Lancet 2002;359:2059-64



TB Risk in HIV-Infected Persons HAART Era

- ART-Linc and the ART Cohort Collaboration
- TB incidence in first year of HAART in low-income (4540 patients) and high-income (22,217 patients) countries
- Incidence much higher in low-income countries, but the ↓ associated with HAART was similar
 - Rate ratio for 7-12 months vs. 1-3 months
 - 0.48 in low-income countries
 - 0.36 in high-income countries

Clin Infect Dis 2007;45:1518-21



Case Presentation # 1 Development of TB after HAART Initiation

- 39 y.o. HIV+ male
- CD4 = 132
- No clinical signs suggestive of TB
- AZT/3TC/lopinavir/ritonavir initiated
- 6 weeks later presents with cough, fever, night sweats, infiltrate on CXR
- Culture-confirmed pulmonary TB



TB After HAART Initiation 5 high-burden countries

- 3,151 patients received HAART
 - Cambodia, Thailand, Kenya, Malawi, Cameroon
- 90% had CD4 < 200
- Median follow-up time: 3.7 – 11.1 months
- Pulmonary TB incidence rate: 4.8-17.6 per 100 p-y
- 62% of pulmonary TB was diagnosed within 3 months after HAART initiation

Does Immune Reconstitution from HAART Increase TB Risk?

- 111 HIV-infected persons with TB—London
 - 19 (17%) were receiving HAART at time of TB diagnosis

	Early (n=13)	Late (n=6)	P
Onset p HAART	41 days	358 days	
CD4 prior to HAART	87	218	.04
IRIS	62%	0%	.02

No difference in rate of change of CD4, VL

TB Risk in HIV-Infected Persons HAART Era—Europe and North America

- Incidence of TB in 1st 3 years of HAART
 - 17,142 ART-naïve AIDS-free persons
 - 173 TB cases: 4.7 per 1,000 person-years
 - TB risk higher if:
 - IDU vs. men-sex-men
 - Lower CD4 at treatment initiation
 - 88 TB cases after 1st 6 months of HAART
 - Low CD4, HIV-1 RNA > 400 copies at 6 months associated with ↑ TB risk

TB Risk in HIV-Infected Persons HAART Era

HAART duration	#TB cases	TB case rate/1000 py
0-3 months	55	13.1
4-6 months	30	7.8
7-12 months	34	4.6
13-24 months	40	3.3
25-36 months	14	1.5

Immune Reconstitution and TB Risk

- Immune reconstitution may make underlying TB more clinically apparent
 - Disease that was not detected prior to HAART initiation (i.e., “unmasking”)
 - Importance of diagnosing sub-clinical TB
- Overall, immune reconstitution due to HAART decreases, not increases, TB risk
- TB risk progressively decreases the longer patients are on HAART

Infectiousness of TB HIV-positive vs. HIV-negative

- Meta-analysis:
 - 10,714 household contacts of TB cases
 - Prevalence of + PPD and active TB similar regardless of HIV status of the index case
Cruciani M. CID 2001;33:1922-30
- Brazil:
 - 104 close contacts of HIV+ pulmonary TB patients
 - 256 close contacts of HIV-neg TB patients
 - Contacts of HIV+ cases less likely to have + PPD or active TB
Carvalho ACC. AJRCCM 2001;164:2166-71

Infectiousness of TB

- In the past, persons did not receive HAART and died shortly after developing TB—and therefore were less likely to transmit *M. tuberculosis*
- With HAART, survival is increased, but so too is the ability to transmit *M. tuberculosis*

Global Incidence of MDR-TB

Resistance to INH + rifampin

- TB cases in 2004
 - Resistance surveys for:
 - New cases (90 countries)
 - Previously treated cases (77 countries)
 - Logistic regression estimated rate among all 184 countries in the world
- Global estimates:
 - 424,203 cases in 2004
 - 4.3% of all new and previously treated TB cases
- China, India, Russian Federation accounted for 62% of estimated global burden of MDR-TB

MDR-TB Rates Among Newly-Diagnosed TB Cases



KwaZulu Natal, South Africa Tugela Ferry

- 119 patients in TB/ARV integration study
 - 14 deaths
 - 10 (71%) of 14 with MDR-TB
 - 6 of 10 MDR-TB resistant to all tested first and second line TB drugs
 - INH, RIF, EMB, STR, KANA, CIPRO
- This uncovered the presence of probable extensively drug resistant TB
- Initiated a cross-sectional study of patients suspected with active TB at rural district hospital
- Isolates collected for mycobacterial culture (MGIT) from January 2005 to March 2006

Characteristics of 53 XDR-TB Patients Representing 10% of isolates tested

<u>Characteristic</u>	<u>No. (%)</u>
• No prior TB Treatment	26 (51)
• Prior TB treatment	
– Cure or Completed treatment	14 (28)
– Treatment Default or Failure	7 (14)
• Identical <i>M. tb</i> spoligotype	26/30
• HIV-infected (44 tested)	44 (100)
• Dead (Includes 34% on ARV)	52 (98)
– Median survival: 16 days from diagnosis	

Commentary

- XDR-TB (like MDR-TB) is iatrogenic
 - Prior treatment, noncompliance, lack of DOT
 - Directly-observed therapy can prevent XDR-TB
- Outbreak in South Africa strikingly similar to MDR-TB outbreaks in the U.S. in 1980s-1990s
 - Nosocomial transmission
 - Must improve infection control
- Use of available infection control strategies could prevent 48% of XDR-TB cases, even in a resource-limited setting (Tugela Ferry)
 - masks, ↓ hospitalization time, improved ventilation, rapid drug resistance testing, HIV treatment, isolation facilities
 - Basu S. Lancet 2007;370:1500-7.

Case Presentation # 2

- A 45 y.o. female active injection drug user with a history of incarceration and HIV presents with a 2-week history of productive cough, night sweats, and weight loss. CXR shows subtle lower lobe infiltrates. She is admitted and placed in respiratory isolation. Three expectorated sputa are AFB-negative.

The patient:

- A. Does not have TB
- B. Should not be started on empiric anti-TB therapy because she has 3 negative AFB smears
- C. Is likely to have a diagnosis of TB established by a positive nucleic acid amplification test
- D. Should be started on 4-drug TB therapy

Smear-negative TB in HIV + Atypical CXR presentation

- Risk is increased in HIV + persons
- Proportion of TB in HIV + persons that is smear-negative pulmonary:
 - 24-61%
 - 15 institution-based studies
 - May be an under-estimate
- Risk of death increased
 - Compared to HIV-negative smear-negative TB patients
 - immunosuppression
 - Compared to HIV-positive smear + TB patients
 - delay in diagnosis

Diagnosis of TB in HIV+ Persons Tanzania

- 14/93 (15%) of HIV+ subjects (CD4 > 200) screened for TB vaccine trial had active TB
 - 10 (71%): clinical TB
 - Symptoms or abnormal CXR
 - 4 (29%): sub-clinical TB
 - +AFB smear/cx but no symptoms and normal CXR
 - 6 more cases subsequently identified
 - Of the 10, 7 identified only by + culture
- Supports use of CXR, sputum culture to rule out TB
 - Generally not done in developing world

Diagnosis of TB in HIV+ Persons United States

- Nashville Metro Public Health Department
 - October 1992-July 2003
 - 601 respiratory culture + TB cases
 - 138 (23%) HIV +
 - Proportion with normal CXR:
 - HIV + : 31/138 (22%)
 - HIV neg/unknown : 22/463 (5%)

P = 0.002
 - Risk factors among HIV+
 - Renal failure, low CD4 (trend)
 - Supports obtaining sputum cx in TB suspects even when normal CXR, particularly in HIV+ persons

Recurrent Tuberculosis Relapse vs. Reinfection

- Recurrent tuberculosis after completion of treatment
 - Relapse: disease with the same *M. tuberculosis* strain as the first episode
 - Related to treatment duration, effectiveness
 - Reinfection: disease with new strain of *M. tuberculosis*
 - Related to TB prevalence in area

Treatment of TB for 6 Months HIV-seropositive vs. HIV-seronegative

<u>Location</u>	<u>Relapse HIV+</u>	<u>Relapse HIV-</u>	<u>Reference</u>
Zaire	9%	5.3%	Perriens NEJM 1995
Cote d'Ivoire	3%	3%	Kassim AIDS 1995
Haiti	5.4%	2.7%	Chaisson AJRCCM 1996
U.S.	3.9%		El-Sadr CID 1998
South Africa	5%	5%	Connolly AIDS 1999
U.S.	6.4%	3%	Sterling AIDS 1999



Treatment of TB in HIV+ Persons Relapse Rates

- 6 months
 - Relapse rate = 6% (range: 3 – 9%)
 - Perriens NEJM 1995
 - Sterling AIDS 1999
 - Fitzgerald Lancet 2000
 - Nahid AJRCCM 2007
 - El-Sadr CID 2001
 - Korenromp CID 2003
 - Nettles CID 2004
- 9 months
 - Relapse rate = 2% (range 1 – 3%)
 - Pulido Arch Intern Med 1997
 - Driver CID 2001



Optimal Duration of TB Treatment Regardless of HIV status

<u>Site of Disease</u>	<u>Duration</u>
Pulmonary	6 months*
Bone/joint	6-9 months
CNS/meningeal	9-12 months
Other extrapulmonary	6 months

*Extend to 9 months if cavitory and culture + at 2 months



Risk Factors for TB Relapse HIV-negative vs. HIV-positive

- Baltimore City Health Department, 1993-2001
- 407 culture + TB patients; 108 (27% HIV+)
- Predictors of relapse if HIV-negative:
 - Cavitory pulmonary disease
 - Culture-positive after 2 months of treatment
 - White race
- Predictors of relapse if HIV-positive:
 - Low CD4 count
 - Median CD4: 51 (recurrence) vs. 138 (no recurrence)

Acquired Rifamycin Resistance USPHS Study 23

- Isoniazid + rifabutin twice-weekly in continuation phase
- 169 patients enrolled
 - 3 treatment failures + 6 relapses; 9/169 = 5.3%
 - 8/9 (89%) acquired rifamycin resistance
- Risk factors for ARR:
 - Twice-weekly therapy during first 2 months
 - Low CD4
 - CD4 < 100: 9/73 (12%)
 - CD4 > 100: 0/65 (0%) P < 0.01

Recommendations for Treatment of TB in HIV-Infected Patients

- TB/HIV patients with CD4 < 100 should not receive once- or twice- weekly therapy
 - Daily therapy during induction
 - Daily or thrice-weekly therapy during continuation

Treatment of TB/HIV Possible Uses of Rifampin (600 mg)

- RIF + efavirenz (consider 800 mg)
- RIF + ritonavir 600 mg bid
- RIF + lopinavir (400 mg) + ritonavir (400 mg)
 - Concern re: hepatotoxicity
- Above regimens must also include NRTIs

- Do not use rifampin with other PIs, even if the PI is given with ritonavir



MMWR 2000;49:185-9. CID 2004;38:426-9. As of Jan 2004 (updated Apr 2007): http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm

Rifampin-Nevirapine

- Rifampin lowers nevirapine levels by 37-58%
- However, 3 small studies demonstrated favorable clinical and virologic response
 - Ribera E JAIDS 2001. Olivia J AIDS 2003. Manosuthi CID 2006.
- No clinical, pk, safety studies assessing increased nevirapine dose with rifampin
- Consider NVP + RIF only when no other options available and close clinical and virologic monitoring can be performed



http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm

Rifampin + RTV/SQV Hepatotoxicity

- Rifampin 600 mg daily +
Ritonavir 100 mg + saquinavir 1000 mg bid
- 11/28 (39%) developed heptox within 28 days
 - Transaminases > 20x upper limit normal
 - One patient required hospitalization
 - Recommend that this combination not be given, even with RTV/SQV 400 mg/400 mg bid



Roche Pharmaceuticals. February 2005.
DHHS Guidelines (<http://aidsinfo.nih.gov>). April 7, 2005

Treatment of TB/HIV Dose Adjustments for Rifabutin

- Rifabutin 150 mg/day (or 300 mg 3x/wk) +
 - nelfinavir 1250 mg bid or 1000 mg tid
 - indinavir 1000 mg q 8
 - amprenavir or fos-amprenavir
- Rifabutin 150 mg qOD or 3x/week +
 - atazanavir
 - ritonavir
 - lopinavir/ritonavir
 - any protease inhibitor boosted by ritonavir



http://www.cdc.gov/tb/TB_HIV_Drugs/default.htm

Treatment of TB/HIV Dose Adjustments for Rifabutin

- Rifabutin 450 mg/day (or 600 mg 3x/wk) +
 - efavirenz 600 mg q D
- Rifabutin 300 mg/day (or 300 mg 3x/wk) +
 - nevirapine 200 mg bid
- All regimens must also include NRTIs



Treatment of TB/HIV Drug Interactions

- Avoid these combinations:
 - rifampin + : saquinavir, indinavir, nelfinavir, amprenavir (fos), atazanavir, tipranavir, darunavir or delavridine
 - rifabutin +: delavridine, saquinavir
- Nucleoside/tide reverse transcriptase inhibitors and enfuvirtide (T20) not affected rifamycins, so can be given



Treatment of TB/HIV New Agents

- CCR5 inhibitors (maraviroc)
 - Rifampin ↓ maraviroc C_{min} by 78%
 - ↑ in maraviroc dose to 600 mg bid may help, but no clinical experience
 - Interactions with rifabutin not studied
- Integrase inhibitors (raltegravir)
 - Rifampin ↓ raltegravir serum levels by 50%
 - Should not use rifampin + raltegravir in combination
 - Interactions with rifabutin not studied

Immune Reconstitution Inflammatory Syndrome

- Clinical Manifestations
 - Constitutional: fever, weight loss,
 - Pulmonary: cough, increased infiltrates
 - Extrapulmonary:
 - Lymphatic: increased cervical, intra-thoracic, intra-abdominal adenopathy
 - Serositis: pleural, pericardial effusions
 - CNS: expanding tuberculomas
 - Other: soft tissue, bone abscesses, skin, +PPD
 - Smear-positive, culture-negative

Immune Reconstitution Inflammatory Syndrome

- First described in treatment of TB in HIV-negative persons: CNS, lymphatic disease
- Differential diagnosis:
 - drug resistance, low drug levels due to malabsorption or interactions, non-adherence, drug fever, lymphoma
- Risk appears to be increased in HIV+ persons, particularly those receiving HAART
 - Risk on HAART 8-43%

Risk Factors for IRIS

In (roughly) decreasing order of importance

- HAART initiation within 2 months of starting anti-tuberculosis treatment
- Disseminated/extrapulmonary TB
- Low baseline CD4 (< 100/mm³)--trend, but consistent
- Increase in CD4% on HAART
- HIV-1 RNA decline on HAART
- Antiretroviral therapy-naïve

Narita 1998, Wendel 2001, Navas 2002, Breen 2004, Breton 2004, Burman 2004, Shelburne 2005



Impact of IRIS on Outcome

- 180 HIV+ patients on HAART—Houston, TX
- 32% developed IRIS (TB, MAC, Cryptococcus)

• Relative risk if IRIS vs. no IRIS:	<u>RR</u>	<u>P</u>
↑ CD4 by > 100 over baseline:	2.2	0.003
HIV-1 RNA < 400 at 24 mos:	3.3	<0.001
Alive 24 mos after HAART start:	2.0	0.06



Shelburne SA. AIDS 2005;19:399-406

When to Start Antiretroviral Therapy in TB/HIV Patients

- Factors to consider:
 - High mortality rate in TB/HIV patients
 - TB accelerates HIV disease progression, death
 - Beneficial impact of HAART on TB/HIV
 - HAART increases CD4 and could ↓ relapse risk
 - Large pill burden for TB and for HIV regimens
 - Drug-drug interactions, toxicity
 - Immune reconstitution inflammatory syndrome (IRIS)



When to Start Antiretroviral Therapy in TB/HIV Patients

- No data from randomized trials
- Results from decision analysis:
 - TB/HIV patients with CD4 < 200
 - Risks and benefits greatest
 - Start HAART < 2 months vs. 2-6 months after TB Rx start
 - Endpoints:
 - Mortality
 - Mortality + AIDS-defining event + severe IRIS + severe AE
 - Early HAART favored
 - Even if IRIS = 70% + severe AE = 56%
 - Except: when IRIS-related mortality > 4.6%

Case Presentation # 3

- A 41 y.o. male was found to be HIV+ on HIV screening during a visit to the emergency room. He is referred to the local HIV clinic for care.
 - CD4+ lymphocyte count = 513
 - HIV-1 RNA = 17,400
- Should he receive a screening TST?

Guidelines for Preventing Opportunistic Infections in HIV+ Persons

- "When HIV is first recognized, the patient should receive a tuberculin skin test."
- "All HIV+ persons, regardless of age, with a + TST (≥ 5 mm induration) but no evidence of active TB and no history of treatment for active or latent TB should be treated for latent TB infection."
 - USPHS, IDSA. Ann Intern Med 2002;137:435-78
- "HIV-infected patients should be tested for *M. tuberculosis* infection by TST."
- "Annual testing should be considered for those with negative TST but who are at high risk for TB exposure"
 - HIVMA, IDSA. Clin Infect Dis 2004;39:609-29.

Latent TB Infection and HIV Switzerland

- Swiss HIV Cohort Study
- Jan 1996 – Feb 2006; 6,160 participants
- 69% had tuberculin skin testing
- 56 TB cases in 25,462 p-y of follow-up
 - 220 per 100,000 p-y
- None of the 193 persons who received treatment of latent infection (TLTBI) developed TB
- Among 246 patients with + TST but no TLTBI, 16 (6.5%) developed TB
- Authors conclude: TST screening, treatment effective



Elzi L. Clin Infect Dis 2007; 44:94-102.

Preventable TB in HIV+ Persons United States

- Seattle, New Orleans, Jersey City (Lee LM. IJTL 2006;10:209-14)
 - June 1995-June 1997
 - 841 HIV +, TST-eligible persons
 - 401 (48%) had TST placed and read
 - 27/401 (6.7%) TST +, and only 16/27 (59%) received treatment
- Nashville, TN (Pettit A. CROI 2007. Abstract 849)
 - ≥ 2 visits to HIV clinic (CCC): Jan 1998 – Dec 2005
 - 3,605 persons in care (12,705 p-y of follow-up)
 - 31 TB cases in 28 patients
 - TB case rate: 244 / 100,000 p-y
 - Of 28 patients, 20 did not have TST as part of routine screening
 - 16 patients developed TB on HAART
 - 4 occurred < 90 days after HAART start (unmasking)
 - » 1 had TST as part of routine screening
 - 20 + 1 = 21/28 (75%) TB cases were potentially preventable



HAART and INH TB Prevention in HIV

- Rio de Janeiro, Brazil
- 11,026 HIV + persons receiving care at 29 public clinics, Sept 2003-Sept 2005

Intervention	TB per 100 p-y
No ART/no INH	4.01
ART	1.90
ART and INH	0.80

- After adjusting for age, previous TB, and baseline CD4, 76% ↓ in TB risk compared to no ART/no INH



Golub J. AIDS 2007;21:1441-8.

Conclusions and Areas of Importance

- HIV responsible for global TB resurgence
- Drug-resistant TB risk ↑ in advanced AIDS
- Must improve diagnosis of TB in HIV + persons
- Optimal treatment duration?
- Optimal timing of HAART initiation in TB/HIV?
- Be aware of TB/HIV drug interactions
 - Dosing recommendations, particularly with new ART
- Importance of latent TB infection: diagnosis, treatment

Restored immune responses on HAART Implications for TB Control

- HIV ↑↑ TB risk: recent exposure, latent infection
- HAART decreases TB risk, but still higher than in HIV-negative persons
- Suggests that immune responses to *M. tuberculosis* are only partially restored
 - Full restoration of CD4 count in minority of patients
 - Even when full repletion, phenotypic abnormalities and functional defects in lymphocytes often persist
- Patients on HAART live longer but still appear to be at ↑ TB risk

Rifampin-Efavirenz

- Rifampin ↓ efavirenz AUC by 25%
 - Consider ↑ efavirenz to 800 mg qD
 - CDC, NIH. MMWR 2004;53:RR-15
- India: 255 HIV+ patients with CD4 ≤ 200
 - All: EFV 600 mg; 126 (TB) also rifampin 600 mg
 - Same clinical, immunologic response
 - Patel A et al. JAIDS 2004;37:1166-9
- Thailand: 84 TB/HIV patients; mean weight 50 kg
 - EFV 600 mg vs. 800 mg: similar EFV levels and outcomes
 - Manosuthi W. AIDS 2005;19:1481-6.
- South Africa: 19 TB/HIV EFV 600 mg + rifampin 600 mg
 - EFV levels varied but good clinical outcomes
 - Friedland G et al. JAC 2006;58:1299-302.

IRIS

Immune Reconstitution Inflammatory Syndrome

- Immune reconstitution is associated with restoration of *M. tuberculosis* antigen-specific CD4+ T-cell responses
- Restoration of response is delayed, and remains lower than in HIV-negative persons, even after months of HAART
- Management is symptomatic relief, and varies according to the severity of manifestations

Optimal Strategy for TB Control in Areas of High HIV Prevalence

- Compartmental difference equation model
- Compared:
 - TB treatment vs. 3 prevention strategies
 - HAART
 - Treatment of latent TB infection
 - Reduction of HIV transmission
- Conclusion:
 - Finding and treating TB most effective way to ↓ TB cases and deaths over 10 years. Prevention strategies must be in addition to TB treatment
